Supreme Court, U.S.
FILED
MAR 22 2005
OFFICE OF THE CLERK

No. 03-1237

IN THE

Supreme Court of the United States

MERCK KGAA,

Petitioner,

v.

INTEGRA LIFESCIENCES I, LTD., and THE BURNHAM INSTITUTE,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

RESPONDENTS' BRIEF ON THE MERITS

MAURICIO A. FLORES
MCDERMOTT WILL & EMERY LLP
18191 Von Karman Avenue
Suite 400
Irvine, CA 92612-7107
(949) 851-0633

DAVID M. BECKWITH
MCDERMOTT WILL & EMERY LLP
4370 La Jolla Village Drive
San Diego, CA 94304
(858) 535-9001

RAPHAEL V. LUPO
Counsel of Record
CATHRYN CAMPBELL
MARK G. DAVIS
M. MILLER BAKER
RICHARD B. ROGERS
MCDERMOTT WILL & EMERY LLP
600 13th Street, N.W.
Washington, D.C. 20005
(202) 756-8000

March 22, 2005

Attorney for Respondents

QUESTION PRESENTED

Whether the District Court properly instructed the jury that, to establish the affirmative defense to patent infringement set forth in 35 U.S.C. § 271(e)(1), Petitioner Merck had the burden "of proving that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question."

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INTRODUCTION

This case lies at the intersection of patent law and the drug approval process under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq*. At that intersection, patent holders have the right of way under the general rule that unauthorized uses of a patented invention constitute infringement. 35 U.S.C. § 271(a). Congress has provided, however, that where a drug manufacturer can prove that its otherwise infringing uses were "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs," 35 U.S.C. § 271(e)(1) ("FDA Exemption"), such uses are exempt and patent holders must yield. Precisely because patent holders have the general right of way at this intersection, however, drug manufacturers must proceed with caution to establish their right to invoke the FDA Exemption and to avoid a collision with the rights of patent holders.

On this record, Petitioner Merck KGaA ("Merck") did not proceed with caution in the face of patent rights held by Respondents Integra Lifesciences I, Ltd. ("Integra"), and The Burnham Institute ("Burnham"). This case did not arise from a decision by Merck to perform experiments designed to satisfy FDA regulatory requirements—that work was done by Merck in Germany and is not the subject of this action. This case arose from Merck's reckless decision to hire The Scripps Research Institute ("Scripps") to embark on a basic research program to search for new drugs. The new drugs infringed pioneering patents owned by Burnham that were exclusively licensed to Integra, but Merck refused to take a license to use the inventions. Scripps, which focuses on the investigation of fundamental disease processes, was not institutionally competent to meet FDA requirements, and the preclinical data it generated had no bearing on the FDA's regulatory approval process. Merck merely used the FDA

Exemption as a pretext to shield infringing research by Scripps while performing the required FDA safety studies itself at its FDA-certified laboratories. Faced with these facts, and with Merck's witnesses discredited at trial, the jury not surprisingly concluded that Merck failed to carry its burden of proving that the infringing experiments were protected by the FDA Exemption.

In the Federal Circuit, Merck challenged the legal standard that it had proposed for the District Court's jury instruction, rather than contesting the sufficiency of the evidence under that standard. Merck argued that the FDA Exemption broadly encompasses all basic research that is a "rational predicate" to the development of data for the FDA.

Rebuffed by the Federal Circuit, Merck petitioned this Court for certiorari on the basis of the extreme legal standard it advanced in the Federal Circuit—that the FDA Exemption encompasses all basic drug research. Now that this Court has granted certiorari, Merck backpedals and disclaims the legal standard that it advanced in the Federal Circuit. Instead, Merck embraces the legal standard that it agreed to in the District Court, and vaguely seeks from this Court the sufficiency of the evidence review of the jury's verdict that it declined to seek from the Federal Circuit—even though Merck's merits brief never once uses the phrase "sufficiency of the evidence," and even though Merck's petition for certiorari never raised or even alluded to the sufficiency of the evidence supporting the jury's verdict.

Given that the parties agree that the District Court's jury instruction applied the correct legal standard, and given that Merck did not seek a sufficiency of the evidence review of the jury's verdict in its petition for certiorari, there is essentially no controversy for this Court to adjudicate. This Court should affirm the Federal Circuit's judgment affirming the

District Court's denial of Merck's renewed motion for judgment as a matter of law ("JMOL") on the FDA Exemption.

Pharmaceutical companies that seek a safe harbor under the FDA Exemption for preclinical work in their own laboratories in compliance with FDA regulations have nothing to fear from the jury verdict or the Federal Circuit opinion, properly understood. Merck's problems in this case are of its own making and are unique to it.

STATEMENT OF THE CASE

The FFDCA's Two-Stage Drug Approval Process

Because the issue in this case is whether Merck has carried its burden of proving that the Scripps experiments were "reasonably related" to the drug approval process, Integra begins with a review of that process. The FFDCA and its implementing regulations establish a two-stage regulatory approval process for new drugs in the United States. The first stage involves an "Investigational New Drug" ("IND") application; the second stage involves a "New Drug Application" ("NDA").

The Role of "Preclinical" and "Clinical" Data in the FDA Drug Approval Process

In the drug approval process, there are two types of drug testing: "preclinical" and "clinical." "Preclinical" testing means testing in test tubes or other artificial settings (*in vitro*) or in living animals. *See* FDA, *Pre-Clinical Research*, http://www.fda.gov/ cder/handbook/preclin.htm. "Clinical" tests or trials, on the other hand, means tests involving human beings. *See* 21 C.F.R. § 312.3(b).

The FDA distinguishes between the use of preclinical and clinical data in the drug approval process. As discussed

below, the FDA reviews preclinical data that has been obtained from laboratories certified as compliant with the FDA's "Good Laboratory Practices" to determine whether a drug candidate is safe enough to proceed to clinical trials. The clinical trials are the basis for further testing on safety, and additionally, efficacy—i.e., does the drug perform as intended with respect to the condition treated? The FDA distinguishes between preclinical and clinical data in the drug approval process:

> The purpose of preclinical work—animal pharmacology/toxicology testing—is to develop adequate data to undergird a decision that it is reasonably safe to proceed with human trials of the drug. Clinical trials represent the ultimate premarket testing ground for unapproved drugs. During these trials, an investigational compound is administered to humans and is evaluated for its safety and effectiveness in treating, preventing, or diagnosing a specific disease or condition. The results of this testing will comprise the single most important factor in the approval or disapproval of a new drug.

FDA, *Clinical Studies (Overview)*, http://www.fda.gov/cder/handbook/clinstud.htm.

Although preclinical data is used to assess safety, it is not used to assess efficacy. There is only one narrow situation—not present in this case—where the FDA may consider preclinical data for efficacy purposes. That circumstance arises where "human efficacy studies are not ethical or feasible." 21 C.F.R. § 314.600.

The IND Stage: The FDA Considers Safety and Not Efficacy

A party seeking approval to market a new drug compound must first seek permission from the FDA to begin clinical trials on human beings. *See* 21 U.S.C. § 355(i)(2). An applicant for permission to conduct clinical trials on human beings with a new drug compound must provide:

> (A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, *necessary to assess the safety of the drug for use in clinical investigation*; and (B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

Id. (emphasis added). Section 355(i)(2) focuses on safety, and does *not* require any submission with respect to a drug candidate's efficacy.[1] Section 355(i)(2)'s omission of "efficacy" or "effectiveness" is telling, in that the concept of "efficacy" is found frequently and prominently in the FFDCA's drug approval provisions. *See, e.g.*, 21 U.S.C. § 355(i)(1) (requiring the FDA to promulgate regulations permitting qualified experts "to investigate the safety and effectiveness" of non-approved drugs for approval purposes).

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[1] Remarkably, Merck cites Section 355(i)(2) and 21 C.F.R. § 312.23 for the proposition that "the preclinical phase involves the development of information to satisfy the FDA that the drug is *sufficiently effective* and safe to justify testing as an [IND] in human clinical trials." Merck Br. at 7 (emphasis added). As demonstrated from the statutory text quoted above, nothing in Section 355(i)(2) supports Merck's "*sufficiently effective*" assertion. As demonstrated further below, 21 C.F.R. § 312.23 does not require preclinical data showing effectiveness.

The FDA's implementing regulation for Section 355(i)(2) requires that the sponsor of a drug candidate submit an IND to the FDA before clinical trials may begin. *See* 21 C.F.R. § 312.20. If the FDA does not object to the proposed clinical trials within 30 days of submission of the IND, such trials may proceed. *See* 21 C.F.R. § 312.40(b).

The FDA's requirements for the contents of an IND can only be understood in the context of the three phases of clinical trials that may occur if the IND is not disapproved by the FDA. Phase 1 studies are relatively limited and closely-monitored trials on fewer than 100 persons to "determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, *and, if possible, to gain early evidence on effectiveness*." 21 C.F.R. § 312.21(a)(1) (emphasis added). Phase 2 studies usually involve no more than several hundred persons to evaluate the effectiveness and safety of the drug *Id.* § 312.21(b). Phase 3 studies are "intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug." *Id.* § 312.21(c).

Just as Section 355(i)(2) of the FFDCA focuses on safety-related data for seeking approval to conduct clinical trials, the FDA regulation outlining "[g]eneral principles of the IND submission" also focuses exclusively on safety: "[The] FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." 21 C.F.R. § 312.22(a). Thus, in terms of data actually submitted to the FDA in an IND, only safety-related data are relevant to the decision to begin Phase 1 clinical testing. While efficacy information is relevant to a subsequent IND submission for Phases 2 and 3 of the clinical trials, such efficacy data are derived from the Phase 1 and 2 tests conducted on human beings, not from the Phase 1 preclinical data.[2]

The FDA's regulation governing the content of the IND submission further confirms that the FDA reviews preclinical data in the IND for the safety of the human subjects in Phase 1 of the clinical testing. That regulation requires the IND submission to include "[a]dequate information about *pharmacological* and *toxicological* studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations." 21 C.F.R. § 312.23(a)(8); *see also* A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION 96 (K. Piña and W. Pines eds., 1998); Addendum, page 8a.

The FDA requires applicants for an IND to submit either preclinical data generated in compliance with well-defined Good Laboratory Practices ("GLP") or a statement of reasons for noncompliance. 21 C.F.R. § 312.23(a)(8)(iii). GLP requirements apply to all "nonclinical studies," which are defined as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions *to determine their safety*." 21 C.F.R. § 58.3 (emphasis added). In practice, applicants for an IND are expected to meet GLP requirements. *See* HOW TO WORK WITH THE FDA: TIPS FROM THE EXPERTS 2 (W. Pines ed., 2000).

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[2] *See* E. WHITMORE, DEVELOPMENT OF FDA-REGULATED MEDICAL PRODUCTS 45 (2004) ("The drug company must first convince the FDA that the drug is reasonably safe *to use in humans to evaluate safety and efficacy* in clinical trials. This is established through preclinical (that is, nonhuman) laboratory testing, including testing in animals.") (emphasis added)

The FDA's Interest in Related Compounds Is Limited to Safety Considerations

Merck asserts that by regulation an IND requires "information not only on the particular compound proposed, but also, as relevant, on 'related drugs.'" Merck Br. at 48 (citing 21 C.F.R. § 312.23(a)(5)(v)). Section 312.23(a)(5)(v) requires that the Investigator's Brochure include "a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs." Thus, related compounds are relevant only to the issue of safety, and then only for the Investigator's Brochure, not the IND itself. The IND itself does not require any *preclinical* data on other compounds, although it does require information of "risks of particular severity or seriousness anticipated on the basis of . . . prior studies in humans with the drugs or related drugs." 21 C.F.R. § 312.23(a)(3)(iv)(f).

Grounds for Disapproval of an IND

Under the FFDCA, the FDA may disapprove an IND and thus bar Phase 1 clinical trials by issuing a "clinical hold." 21 U.S.C. § 355(i)(3)(A). Such a clinical hold may be issued when "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." *Id.* § 355(i)(3)(B). Nothing in the statute requires consideration of efficacy; instead, the focus is on risk to the subjects of the trial.

Similarly, Section 355(i)(3)(B)'s implementing regulation does not include efficacy data as a basis upon which to issue a clinical hold. 21 C.F.R. § 312.42(b) (stating that grounds for imposition of a clinical hold include, *inter alia*, (i) "unreasonable and significant risk of illness or injury"); *see also* FDA, *Phase 1 Clinical Studies*, http://www.fda.gov/cder/handbook/phase1.htm.

The NDA Stage: Safety and Efficacy

If all three phases of clinical trials succeed, an applicant then files an NDA pursuant to 21 U.S.C. § 355(b), to include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A). Thus, in contrast to the FFDCA provision governing the IND, which speaks only in terms of safety, *see id.* § 355(i)(2), the FFDCA provision governing the NDA expressly requires data on *both* safety and efficacy.

Similarly, the NDA regulations and the FDA website state that NDA data is reviewed for both safety *and* efficacy. *See* 21 C.F.R. § 314.2 ("The purpose of this part [governing NDA] is to establish an efficient and thorough drug review process in order to: (a) facilitate the approval of drugs shown to be safe and effective; and (b) ensure the disapproval of drugs not shown to be safe and effective."); *Clinical Studies (Overview)*, *supra* ("An NDA must provide sufficient information, data, and analyses to permit FDA reviewers to reach several key decisions, including[w]hether the drug is safe and effective for its proposed use(s), and whether the benefits of the drug outweigh its risks.").

Finally, while the regulations do contain a provision requiring the submission of "nonclinical" data as part of the NDA, 21 C.F.R. § 314.50(d)(2), the regulations define "nonclinical" as referring to preclinical data relating to *safety*. 21 C.F.R. § 58.3(d). Thus, the regulations clarify that the preclinical data are relevant at the NDA stage only for *safety* purposes (aside from in the few cases encompassed by the narrow exception noted above).

The Patents in Suit

In the 1980s, two scientists at Burnham, Drs. Erkki Ruoslahti and Michael Pierschbacher, made a series of pioneering discoveries concerning the mechanism by which cells attach and detach from proteins that form the extracellular matrix in the body. Tr. 333–43. First, they made the surprising discovery that out of the thousands of amino acid combinations that form the extracellular matrix proteins, a sequence of only three amino acids (referred to as "RGD") constitutes the site where cells attach to these proteins. Tr. 824–26. Second, they used synthetic peptides containing the RGD attachment site as a tool to isolate the cellular structures that bind to that site, which turned out to be cell surface proteins with the characteristics of a receptor. Tr. 346–47.

Drs. Ruoslahti and Pierschbacher then identified other members of what turned out to be a genetically-related family of cell surface receptors, previously unknown, that bind to the RGD attachment site. Tr. 350. These cell surface receptors, called integrins, are enormously important because they control myriad cellular functions and processes. In effect, Drs. Ruoslahti and Pierschbacher discovered the key (the RGD sequence) to a lock (the integrin cell surface receptors) that controls a wide range of cellular activity. These discoveries by Drs. Ruoslahti and Pierschbacher spawned an explosion of scientific research related to RGD peptides and integrins. Tr. 362–65, 369, 370–75.

Four patents at issue were granted for these pioneering discoveries.[3] Claim 1 of U.S. Patent No. 4,789,734 (the "'734 Patent") claims a composition containing a cell surface receptor that binds to the RGD attachment site. S.A. 14.

[3] A fifth patent, U.S. Patent No. 4,988,621 (the "'621 Patent"), also covered certain aspects of these inventions; it is not at issue here.

That claim encompasses the $\alpha_v\beta_3$ receptor.[4] Claims 4 and 8 of U.S. Patent No. 4,879,237 (the "'237 Patent") claim methods for detaching animal cells from a substrate. S.A. 16–17. The asserted claims of these patents would not be infringed by the manufacture or sale of the RGD peptide drug composition for which Merck seeks FDA approval. They are useful only as biomedical research tool patents.

Claim 8 of U.S. Patent No. 4,792,525 (the "'525 Patent") claims the composition of non-naturally occurring RGD-containing peptides that have cell attachment activity. S.A. 12. Claims 15 through 18 of U.S. Patent No. 5,695,997 (the "'997 Patent") claim various methods for blocking cell surface receptors. S.A. 19. These claims would be infringed by sale or use of Merck's proposed RGD product.

Collectively, these patented inventions cover not only the compositions of RGD peptides with cell attachment activity and the cell surface receptors to which they bind, but also three distinct ways to manipulate cell interaction with the extracellular matrix: (1) promotion of cell attachment by use of an RGD peptide ('525 Patent); (2) blocking cell attachment ('997 Patent); and (3) disrupting existing cell attachment ('237 Patent). Tr. 361. All of these compositions and methods, regardless of whether they cover a drug product, are useful as tools for biomedical research. This use of RGD peptides to isolate the integrin receptors is a good example of the value of the inventions as research tools.

Drs. Ruoslahti and Pierschbacher founded Telios Pharmaceuticals in June 1987. Tr. 375. Burnham's RGD patents were exclusively licensed to Telios.

[4] The term $\alpha_v\beta_3$ is pronounced "alpha-v-beta-3."

Dr. Cheresh's Discovery That the Integrin $\alpha_v\beta_3$ Controls Angiogenesis

In April 1994, following the path blazed by Drs. Ruoslahti and Pierschbacher, Dr. David Cheresh, a scientist at Scripps, published a paper in *Science* demonstrating that one of the cellular processes controlled by the integrin $\alpha_v\beta_3$ is angiogenesis, the growth of blood vessels. Tr. 1063. Specifically, Dr. Cheresh demonstrated that blocking the $\alpha_v\beta_3$ receptor would inhibit angiogenesis in tumors, depriving them of the blood supply they need to grow. *Id.*

This discovery showed that any one of three types of entities known to block the $\alpha_v\beta_3$ receptor—antibodies, synthetic RGD peptides, or organic molecules that "mimic" the cell attachment activity of the RGD sequence—could be used as a drug therapy that inhibits the growth of solid tumors. Tr. 1080–81. Dr. Cheresh characterized this work as his "major discovery," stating, "That was when we knew what we had." J.A. 190.

Dr. Cheresh's *Science* publication described the use of an antibody to block the $\alpha_v\beta_3$ receptor. Tr. 1063. Subsequently, in December 1994, Dr. Cheresh published a second paper in which he used an RGD peptide for the same purpose. That peptide, denominated 66209, had been provided to him by Merck. In a previous paper, it had been shown that 66203 blocked the $\alpha_v\beta_3$ receptor. Tr. 1072–75.

Merck Imports Infringing Compounds for Scripps' Use and Induces Scripps to Infringe

After learning of Dr. Cheresh's discovery, Merck expressed interest in negotiating a sponsored research agreement with him and Scripps to investigate $\alpha_v\beta_3$ inhibitors. Merck was not interested in pursuing work on antibodies, but

it was interested in research on the two other classes of potential $\alpha_v\beta_3$ inhibitors: RGD peptides and organic molecules that mimic the RGD cell attachment activity. Tr. 1103, 1115–16. Merck had not then decided on what $\alpha_v\beta_3$ inhibitor it would focus its development efforts. On April 13, 1995, Merck's head of Preclinical Research and Development, Dr. Jan Sombroek, wrote to Dr. Cheresh that "Merck will take care of toxological studies once we have defined a product for the pipeline. Pharmacokinetica, pharmacodynamics and biodistribution studies will routinely be performed at our institute in Grafing, unless we ask you to help us because of capacity problems." J.A. 126–27.

In August 1995, Merck and Scripps executed a research funding agreement for the use of peptide and organic molecule inhibitors of $\alpha_v\beta_3$. Dr. Cheresh testified, "[A]t that time we were really searching for an ideal drug candidate." Tr. 1092. To that end, Scripps used RGD peptides as positive controls to assess the anti-angiogenic properties of non-RGD organic molecule mimetics. Tr. 1091, 1092–94. The agreement provided Merck funding to Dr. Nicoloau, a Scripps scientist charged with developing organic molecule mimetics to be tested. This funding of Dr. Nicoloau and testing of his newly developed non-RGD organic compounds were important parts of Merck's strategic objective in funding Scripps' research. Docket No. 1027, Ex. 9, at 91.

Thus, the Scripps research funded by Merck was not limited to RGD peptides. Tr. 1115. Nor was this Merck-funded research strictly limited to the search for an RGD or non-RGD organic compound that blocks the $\alpha_v\beta_3$ receptor. The Merck-funded research was also designed generally to strengthen the "scientific foundation" of the basic approach of blocking the $\alpha_v\beta_3$ receptor to inhibit angiogenesis in tumors. Tr. 1128. As explained by Dr. Cheresh, "[The] idea is to have three separate structural distinct compounds do the

same thing, and that really bolsters the notion that $\alpha_v\beta_3$ is the thing you want to target, whether you do it with a peptide, whether you do it with an antibody, whether you do it with an organic molecule." Tr. 1128–29. Identifying organic molecules that mimic cell attachment activity would enable Scripps to obtain broader patent claims. Tr. 1129.

Under the 1995 agreement, Merck, not Scripps, took responsibility for conducting the expensive experiments necessary to assess toxicity and pharmacokinetics under the FDA's "Good Laboratory Practices" requirements. Merck Br. at 14. As an institution dedicated to basic research aimed at discovering the principles that underlie disease, Tr. 3208, Scripps lacked the expertise and facilities necessary to comply with the GLP requirements for nonclinical research related to safety.

Merck Refuses to Purchase a License from Telios

When Dr. Pierschbacher read Dr. Cheresh's December 1994 article describing the use of an RGD peptide to inhibit angiogenesis, he realized that Scripps' work had passed beyond the basic research stage and had advanced to the point where commercial drug possibilities were being explored. Tr. 416–17. Dr. Pierschbacher also realized that people at Merck with whom he was already in contact were interested in using an RGD peptide as a cancer drug. Tr. 417–19.

Dr. Pierschbacher and others at Telios unsuccessfully tried to convince Merck to work with an RGD compound that Telios was developing. Telios later made clear that, regardless of whether Merck went ahead with Scripps or with Telios, Merck would have to obtain a license to Telios's RGD patents. Tr. 450. At a final meeting with Dr. Pierschbacher in Germany, Merck announced that it had no interest in licensing any rights from Telios and was terminating negotiations. Tr. 450–51.[5]

The District Court Action

Unable to negotiate a license agreement with Merck, Telios and Burnham brought this patent infringement action against Merck in the U.S. District Court for the Southern District of California in 1996. J.A. 10. Integra joined the action as a plaintiff when it acquired Telios's patent rights. (Hereinafter, the plaintiffs are referred to collectively as "Integra.") The suit alleged that Merck, Scripps, and Dr. Cheresh either directly infringed or induced the infringement of five U.S. patents by importing the infringing RGD peptides into the United States and by contracting for their infringing use in evaluating potential drug candidates and general biomedical experiments. *See* Compl., Docket No. 1.

Merck, Scripps, and Dr. Cheresh answered that the experiments at issue were exempt from infringement liability under either the common law research exemption or the FDA Exemption, 35 U.S.C. § 271(e)(1). Under Merck's theory, any research to identify or develop a drug subject to FDA approval would be exempt from patent infringement liability.

Early in the case, Merck moved for partial summary judgment on the FDA Exemption with respect to one of the patents at issue. The District Court agreed with Merck that the FDA Exemption encompassed activities reasonably related to the submission of information for an IND application but denied the motion, finding that triable issues of fact ex-

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[5] Merck asserts that Telios *conditioned* a license upon an agreement from Merck to provide support for developing unrelated drugs, *see* Merck Br. at 21, but that is incorrect. The page Merck cites does not support the assertion.

isted as to whether the Scripps experiments beginning in September 1995 were exempt under the FDA Exemption. J.A. 33–44. The District Court based this ruling in part on inconsistencies in the testimony of Dr. Cheresh and Merck employees. J.A. 37–44.

Before submitting the case to the jury, the District Court partially granted Merck's Rule 50(a) motion for judgment as a matter of law and ruled that all pre-1995 experiments (with the exception of a single experiment performed in August 1994) were exempt under the common law research doctrine. Tr. 3369–91. Integra did not appeal this ruling.[6]

The District Court found that issues of fact precluded judgment as a matter of law that the remaining 180 Scripps experiments conducted from 1994–1998 were covered by the FDA Exemption. Tr. 3391. Accordingly, the District Court submitted the 180 experiments conducted from 1994–1998 to the jury to resolve the factual dispute over whether the FDA Exemption's "reasonable relationship" test was met. The court adopted an instruction that applied a legal standard on which *both* parties agreed and had derived from *Intermedics, Inc. v. Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), *aff'd without op.*, 991 F.2d 808 (Fed. Cir. 1993).[7] The instruction adopted by the District Court incorporated the legal standard proposed by Merck:[8]

[6] The District Court also dismissed the case against Scripps and Dr. Cheresh. The Federal Circuit affirmed this ruling. *See* P.A. 6, 23.

[7] The Federal Circuit had previously approved the *Intermedics* standard. *See Telectronics Pacing Sys., Inc. v. Ventritex, Inc.*, 982 F.2d 1520, 1525 n.5 (Fed. Cir. 1992). District courts have consistently applied *Intermedics* in construing Section 271(e)(1). *See, e.g., Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 108 (D. Mass. 1998).

[8] *See* Docket No. 992, at 14. Although the District Court adopted Merck's proposed *legal standard* for the instruction, the District Court (continued...)

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

J.A. 57. The verdict form emphasized Merck's burden of proof as to the FDA Exemption. The verdict form provided: "Has Defendant Merck KGaA met its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption?" J.A. 62.[9]

did not adopt the entirety of Merck's proposed instruction. Hence, Merck filed objections to the jury instructions. Those objections are not material to the legal standard to which Merck agreed. Indeed, Merck failed to appeal those objections to the Federal Circuit or to note those objections in its certiorari petition or its merits brief.

[9] Merck objected to the jury verdict form and sought an experiment-by-experiment determination of the FDA Exemption, but the District Court overruled the objection, finding that "there wasn't enough support in either the underlying evidence or in final summations upon which the jury could make an adequate and competent decision" on an experiment-by-experiment basis. J.A. 456. Merck later filed a motion for a new trial based on the verdict form, but the District Court correctly denied the motion. The District Court ruled that "the verdict form used was adequate to obtain a jury determination of all factual issues essential to judgment." Docket No. 1135 at 3 (citing *In re Haw. Fed. Asbestos Cases*, 871 F.2d 891, 894 (9th Cir. 1989)). Merck notes its objection in its merits brief to this Court, Merck Br. at 22, but fails to assert any legal error in the District Court's overruling of the objection. Merck also failed to challenge the verdict form in its appeal to the Federal Circuit. Moreover, Merck's certiorari petition failed to raise this issue.

The jury found that Merck willfully infringed and induced infringement of each of the patents in suit. J.A. 63. Applying the legal standard proposed by Merck, the jury found that Merck did not carry "its burden of proving by a preponderance of the evidence that all of the accused activities are covered by the FDA Exemption." J.A. 62. The jury awarded Integra $15,000,000 in damages for Merck's infringing activities. J.A. 62. The District Court entered an amended final judgment on October 6, 2000. P.A. 45–46.

Merck then filed a renewed JMOL motion under Federal Rule of Civil Procedure 50(b) with respect to its affirmative defense under the FDA Exemption. The District Court denied this motion, finding that the record evidence was sufficient to uphold the verdict. P.A. 47–50. Merck also filed a motion for a new trial based on the FDA Exemption. The District Court denied the motion, finding that "there was ample evidence for both the court and the jury to determine that the FDA Exemption did not apply to this action. The clear weight of the evidence supports the verdict, and Merck's arguments do not present grounds for granting a new trial." Docket No. 1135 at 2.

The Federal Circuit Appeal

On appeal to the Federal Circuit, Merck argued that the FDA Exemption encompasses "drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." Merck C.A. Br. at 45. In effect, Merck challenged the legal standard in the jury instruction, even though Merck had agreed with the substance of that instruction, thereby waiving any objection under Federal Rule of Civil Procedure 51.

Rather than rejecting (as waived) Merck's newly-raised challenge to the legal standard found in the jury instruction,

the Federal Circuit panel majority entertained the new legal theory on the merits and emphatically rejected it. The court posed the issue as follows: "[W]hether the § 271(e)(1) safe harbor reaches back down the chain of experimentation to embrace development and identification of new drugs that will, in turn, be subject to FDA approval." P.A. 10. Finding that "the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds," the panel held that "[e]xtending § 271(e)(1) to embrace new drug development activities would ignore its language and context with respect to the 1984 Act in an attempt to exonerate infringing uses only potentially related to information for FDA approval." P.A. 13. Such an expansive reading would, in turn, "vitiate the exclusive rights of patentees owning biotechnology tool patents." P.A. 13–14.[10]

Merck asserts that "[i]n contrast to the District Court, the [Federal Circuit] majority did not review the record for material issues of disputed fact. Rather, the panel concluded, apparently as a matter of law, that the FDA exemption could not apply to any of the experiments remaining in the case." Merck Br. at 23. What Merck fails to acknowledge *is that its own legal theory changed between trial and appeal.*

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[10] The cell surface receptors claimed in the '724 Patent and the methods for detaching animal cells from a substrate claimed in the '237 Patent constitute "tool" patents because their value is in their use as research tools, *see* P.A. 22 n.4 (defining "tool" patents). Therefore, they would not be infringed by the manufacture, use, or sale of the RGD peptide that Merck seeks to market as a drug. Under the legal standard reflected in the District Court's jury instruction, whether infringing uses of tool patents are subject to the FDA Exemption is decided on a case-by-case basis. In the Federal Circuit, however, Merck argued that the FDA Exemption encompassed all basic research for drug development, an argument that the Federal Circuit correctly recognized would extinguish "the whole benefit of the Patent Act for some categories of biotechnological inventions." *See* P.A. 14.

In the District Court, Merck had proposed the essence of the legal standard found in the jury verdict and challenged the sufficiency of the evidence supporting the jury's verdict. In the Federal Circuit, by contrast, Merck *de facto* challenged the legal standard in the jury instruction, arguing that it was entitled to judgment as a matter of law based on that theory, even though its infringing activities were only, in its words, "a rational predicate to moving forward with drug development and to developing information to be submitted to the FDA." Merck C.A. Br. at 2. The reason the Federal Circuit did not engage in a sufficiency of the evidence review, based on the legal standard that Merck had proposed at trial, *was because Merck did not ask it to.* Merck gambled and lost by raising a novel and aggressive legal theory.

Merck's Certiorari Petition

Merck's certiorari petition presented the following question: "Did the Federal Circuit err in concluding that this drug-research safe harbor does not protect animal studies of the sort *that are essential to the development of new drugs*, where the research will be presented to the FDA, and where barring the research until expiration of the patent could mean years of delay in the availability of life-saving new drugs?" Petition at i (emphasis added). With this question, and with certain other statements in the petition, Merck seemingly reasserted its "rational predicate" argument, which the Federal Circuit had squarely rejected. *See* Petition at 14 (asserting that FDA Exemption "provides broad protection to all activities associated with the development of new drugs and medical devices") (internal quotation marks omitted); 17 ("This Court should review this case to decide whether, consistent with the pervasive view before this case, Congress adopted the drug-research safe harbor to promote the development of new drugs, not just to promote generics.").

Nowhere in Merck's petition did it challenge or even raise the sufficiency of the evidence underlying the jury's verdict. Nor is the sufficiency of the evidence supporting the verdict fairly included within the scope of the question upon which certiorari was granted. *Cf. Boyle v. United Techs. Corp.*, 487 U.S. 500, 514 (1988) (declining to undertake sufficiency of the evidence review "since petitioner did not seek from us, nor did we grant, review of the sufficiency-of-the-evidence determination"); *Wash., Va., & Md. Coach Co. v. NLRB*, 301 U.S. 142, 146 (1937).

Merck Backpedals from the Question Presented

In its merits brief, Merck clearly retreats from the question upon which certiorari was granted. Rather than the broad "rational predicate" argument it advocated in the Federal Circuit—and seemingly asserted in its petition—Merck's merits brief asserts that the question presented is whether the FDA Exemption "protect[s] the animal and test-tube studies that typically accompany an application to the FDA to allow a new drug to proceed to clinical trials in humans." Merck Br. at i. This question is considerably narrower because the focus is limited to the information submitted to the FDA to allow clinical testing in humans, rather than, as Merck's certiorari petition phrased the question, in "animal studies that are essential to the *development of new drugs*." Petition at i (emphasis added). Indeed, in its merits brief Merck expressly disclaims applying the FDA Exemption to "basic exploratory research or screening of untested structures in test tube." Merck Br. at 40; *see also id.* at 37 (arguing that this Court need not go so far as *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 2001 WL 1512597 (S.D.N.Y. 2001), which holds that all drug research is protected by the safe harbor); *cf.* Merck C.A. Br. at 46 (urging Federal Circuit to follow *Rhone-Poulenc*).

Thus, Merck's merits brief abandons the "rational predicate" standard it asserted both before the Federal Circuit and as the basis of the question presented in its certiorari petition. Embracing the legal standard it proposed in the District Court but spurned in the Federal Circuit, Merck now appears to seek from this Court the sufficiency of the evidence review that it failed to seek from the Federal Circuit.

SUMMARY OF THE ARGUMENT

Merck has retreated from the question presented in its certiorari petition. Rather than arguing the FDA Exemption encompasses all basic drug research that is a "rational predicate" to the development and submission of information to the FDA, as Merck argued before the Federal Circuit and seemingly argued in its certiorari petition, Merck focuses on the Federal Circuit's distinction between preclinical and clinical research. Merck extrapolates from that language a supposed bright line rule that excludes *all* preclinical research from the scope of the FDA Exemption, including preclinical data required to be submitted with an IND in the first stage of the drug approval process.

The Federal Circuit's holding was not so broad. Read as a whole, especially in the context of the extreme argument advanced by Merck, the Federal Circuit opinion merely holds that *Merck's* preclinical experiments, which *Merck* characterized as "logical predicates to moving forward with the drug development and to developing information to be submitted to the FDA," Merck C.A. Br. at 50, are not protected by the FDA Exemption.

More importantly, the language of the Federal Circuit opinion is ultimately immaterial to the disposition of this case. What is before this Court is the judgment of the Federal Circuit affirming the District Court's order denying Merck's motion under Federal Rule of Civil Procedure 50(b)

for JMOL on the FDA Exemption. This Court reviews judgments, not opinions. *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984). That judgment should be affirmed.

First, Merck does not challenge the legal standard in the District Court's jury instruction, the substance of which Merck proposed in the District Court. That legal standard assumes that the FDA Exemption encompasses preclinical data, so long as the data are reasonably related, relatively directly, to either the IND or NDA stages of the drug approval process. The parties agree that the legal standard in the jury instruction was correct.

Merck's certiorari petition did not raise the sufficiency of the evidence supporting the jury's verdict. Merck's merits brief, however, vaguely appears to seek a sufficiency of the evidence review of the District Court's order denying Merck's renewed JMOL, although Merck fails to cite Rule 50, to address the applicable standard of review, or even to use the phrase "sufficiency of the evidence." If, indeed, Merck seeks a sufficiency of the evidence review of the jury's verdict based on the legal standard reflected in the jury instruction, then this Court should deny it because it was not asserted in the petition for certiorari, and because it was waived by Merck's failure to seek such review in the Federal Circuit.

Thus, this Court should affirm the Federal Circuit's judgment affirming the District Court's order denying Merck's JMOL on the basis that (1) the parties agree that the legal standard in the jury instruction was correct and (2) Merck failed to raise the sufficiency of the evidence supporting the jury verdict in its petition for certiorari. Given these facts, there is no controversy remaining for this Court to adjudicate.

If this Court undertakes the Rule 50 sufficiency of the evidence review that Merck appears to seek, then this Court must consider only Integra's evidence and that portion of Merck's evidence that the jury was required to believe. In reviewing the evidence, this Court is required to give every reasonable favorable inference to Integra.

When the evidence is reviewed under the appropriate standard, it is clear that a sufficient evidentiary basis supported the jury's verdict that Merck failed to carry its burden under the jury instruction of establishing that the Scripps experiments "would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." J.A. 57. This is particularly true given that most of Merck's witnesses were discredited and the jury understood that Merck, not Scripps, was performing the safety studies required by the FDA for an IND.

The relevant provisions of the FFDCA and its implementing regulations demonstrate that the FDA reviews preclinical data submitted in an IND for safety purposes only. Such data must be produced by laboratories that comply with the FDA's GLP standards. Scripps' laboratories were not GLP-certified, which is why Merck planned to do the FDA safety-related work at its own laboratories, which were GLP-certified. Moreover, most of the experiments were on models (e.g., chicken embryos) *not* predicative of human safety. Thus, substantial evidence supports the jury's conclusion that the Scripps experiments were not reasonably related, relatively directly, to the submission of safety data to the FDA.

Even if the FDA considered preclinical data for efficacy, the jury could reasonably infer from the evidence that many, if not most, of the Scripps experiments had no bearing on

efficacy. First, the jury could reasonably infer that Scripps' chicken embryo experiments that had no predicative value for human safety also had no predicate value for human efficacy. Second, because most of Scripps' witnesses were discredited, the jury was simply not obligated to believe their testimony that the experiments generated efficacy data.

ARGUMENT

I. MERCK AND THE GOVERNMENT MISREAD THE FEDERAL CIRCUIT OPINION, BUT, REGARDLESS OF HOW THE OPINION IS READ, THERE IS NO PRESENT CONTROVERSY OVER THE FEDERAL CIRCUIT'S JUDGMENT.

Both Merck and the government argue that the Federal Circuit decision, by distinguishing between Merck's "preclinical" and "clinical" activities, excludes preclinical data submissions for an IND from the scope of the FDA Exemption. This argument misreads the Federal Circuit opinion.

First, this argument overlooks the context of the Federal Circuit decision. Merck's principal argument before the Federal Circuit was that the FDA Exemption encompasses "drug development research that serves as a rational predicate to generating information for submission to the FDA, including any tests conducted to determine whether to proceed with a drug candidate." Merck C.A. Br. at 45. This amounted to a *de facto* challenge to the legal standard in the jury instruction that Merck proposed in the District Court. Rather than dismissing Merck's argument out of hand on the basis of waiver, the Federal Circuit considered and rejected it on its merits. Thus, in stating that "[t]he safe harbor does not reach any exploratory research that may rationally form a predicate for future FDA clinical tests," P.A. 13, the Federal Circuit was responding to Merck's argument that "drug development activities meet the statutory exemption if they

served as a rational predicate to moving forward with the drug development and to developing information to be submitted to the FDA." Merck C.A. Br. at 47.

Second, the Federal Circuit opinion does not expressly distinguish between the IND and NDA stages of the drug approval process. Instead, the opinion focuses on the general FDA drug approval process, which necessarily encompasses both the IND and NDA stages. *See, e.g.*, P.A. 11 ("[T]o qualify at all for the exemption, an otherwise infringing activity must reasonably relate to the development and submission of information for [the] FDA's *safety and effectiveness approval processes*. The focus of the entire exemption is the provision of information to the FDA." (emphasis added)). Because the IND application relates to the drug candidate's safety, this passage can be understood only as supporting the proposition that IND-related activities fall within the scope of the exemption. *See also* P.A. 9 (stating that the FDA Exemption covers "activities . . . reasonably related to securing *regulatory approval*." (emphasis added)).

Indeed, the panel expressly stated that the FDA Exemption encompasses the IND. *See* P.A. 12 ("In this case, the Scripps work sponsored by Merck was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds. The FDA has no interest in the hunt for drugs that may or may not later undergo clinical testing for FDA approval. *For instance, the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application.*" (emphasis added)). This passage can only mean that IND-related information (and thus preclinical information) is subject to the exemption.

When read as a whole, and especially in the context of Merck's "rational predicate" argument, the Federal Circuit opinion holds that *Merck's* preclinical work *in this case* falls

outside the scope of the exemption because it is, as the jury found, not reasonably related to submission of data for an IND. *See* P.A. 10 ("The *Scripps–Merck experiments* did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA processes." (emphasis added)). The opinion should not be read as holding that *all* preclinical activities are *per se* outside the scope of the exemption.

Nevertheless, if the Federal Circuit opinion actually means what Merck and the government say it means, Integra does not defend it. It would be contrary to the legal standard in the District Court's jury instruction and to what the parties and the District Court understood, especially given that the District Court ruled early in the case that the FDA Exemption applied to the IND stage of the drug approval process. *See* J.A. 37. In the District Court, the case was tried, and the jury was instructed, on the assumption that the FDA Exemption applied to the IND stage of the drug approval process.

Any legal error in the Federal Circuit's opinion with regard to the preclinical/clinical distinction, however, is of no moment to this Court's disposition of this case. This Court reviews "judgments, not statements in opinions." *Black v. Cutter Labs., Inc.*, 351 U.S. 292, 297 (1956); *see also Chevron*, 467 U.S. at 842. The judgment of the Federal Circuit under review affirmed the District Court's order denying Merck's renewed JMOL under Federal Rule of Civil Procedure 50(b). There is no present controversy over whether that *judgment* is correct.

There is no present controversy between the parties because they agree that the District Court's jury instruction applied the correct legal standard. Merck proposed that legal standard in the District Court, but challenged the standard in the Federal Circuit and in its petition for certiorari in this Court with its argument that basic drug research activities are

covered by the safe harbor. In its merits brief, however, Merck abandons that challenge and now argues that the Federal Circuit did not apply the legal standard that the parties agree the District Court correctly applied.

Merck's merits brief appears to raise a sufficiency of the evidence challenge to the jury's verdict that Merck did not carry its burden of proof under the FDA Exemption. Merck's petition for certiorari, however, did not raise the sufficiency of the evidence supporting the jury's verdict or seek review on that ground. Because the parties agree that the District Court's jury instruction applied the correct legal standard, and because Merck is now foreclosed from challenging the sufficiency of the evidence supporting the jury's verdict under that agreed-upon legal standard, it necessarily follows that there is no present controversy between the parties over the Federal Circuit's judgment affirming the District Court's order denying Merck's renewed JMOL. Thus, this Court should affirm the Federal Circuit's judgment, even if this Court ultimately disapproves of the precise language or rationale of the Federal Circuit opinion.

II. THE DISTRICT COURT'S JURY INSTRUCTION APPLIED THE CORRECT LEGAL STANDARD, WHICH MERCK PROPOSED IN THE DISTRICT COURT AND DOES NOT CHALLENGE HERE.

Congress limited the FDA Exemption to activities that are "solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Although Section 271(e)(1) is hardly "an elegant piece of statutory draftsmanship," *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 679 (1990), there are at least four inferences that a court must draw from this text.

First, Congress manifestly eschewed a bright line test for demarcating the boundaries of the FDA Exemption. Instead, Congress defined the exemption in terms of "uses reasonably related to the development and submission of information under a federal law." Whether otherwise infringing uses are "reasonably related" to the development and submission of information to the FDA will depend upon the particular facts and circumstances of the infringing uses in relation to the FDA approval process. *See* BLACK'S LAW DICTIONARY 1265 (6th ed. 1990) (defining "reasonable" as "[f]air, proper, just, moderate, suitable under the circumstances. Fit and appropriate to the end in view."); *cf. Skinner v. Ry. Labor Executives' Ass'n*, 489 U.S. 602, 619 (1989) (finding that in the context of the Fourth Amendment's guarantee against "unreasonable" searches, "[w]hat is reasonable, of course, depends on all of the circumstances" (internal quotation marks omitted)). This is essentially a fact-bound determination that will turn upon the particular nature of the infringing uses in relation to the development and submission of information to the FDA. *Cf. City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 721 (1999) (holding, in a regulatory takings case, that whether a city's decision to reject a particular development plan bore a "reasonable relationship" to its proffered justification was a fact-bound question properly submitted to the jury).

Second, by employing the term "reasonably related," Congress specified an objective, rather than subjective, standard. *See Intermedics*, 775 F. Supp. at 1279 ("'Reasonably related' is language that clearly has become associated with objective standards.").

Third, Section 271(e)(1) is an exception to the general rule of liability for patent infringement. 35 U.S.C. § 271(a) ("*Except as otherwise provided in this title*, whoever without authority makes, uses, offers to sell, or sells any patented invention . . . infringes the patent." (emphasis added)). As a

statutory exception, Section 271(e)(1) should be read narrowly to preserve the general rule. *See Commissioner v. Clark*, 489 U.S. 726, 739 (1989) (noting that where "a general statement of policy is qualified by an exception, we usually read the exception narrowly in order to preserve the primary operation of the provision"). To emphasize the exemption's limited scope, Congress prefaced it with the word "solely." Although lower courts have disagreed over the exact import of the word "solely," *see Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 3 F. Supp. 2d 104, 107–08 (D. Mass. 1998) (reviewing cases), Congress's use of the word clearly signals that Section 271(e)(1)'s scope is not unlimited and that the section certainly does not provide a broad exemption for basic drug research and development. As the Federal Circuit observed, "The term 'solely' places a constraint on the inquiry into the limits of the exemption. The exemption cannot extend at all beyond uses with the reasonable relationship specified in § 271(e)(1)." P.A. 11.[11]

Finally, the Section 271(e)(1) exception was intended to be *limited*, and, thus, a party invoking Section 271(e)(1) as an affirmative defense to liability for infringement under Section 271(a) has the burden of proof. *See NLRB v. Ky. River Cmty. Care, Inc.*, 532 U.S. 706, 711 (2001) (noting that "the burden of proving justification or exemption under

[11] The legislative history of Section 271(e)(1) further underscores that the exemption was not meant to broadly eliminate patent rights. The House Judiciary Committee report stated that the "nature of interference with the rights of the patent holder is not substantial." *See* H.R. REP. NO. 98-857, pt. 2, at 8, *reprinted at* 1984 U.S.C.C.A.N. 2692. Indeed, later in the report the effect of Section 271(e)(1) was characterized as "de minimus [sic]." *Id.* at 2714. Although this Court has noted that Section 271(e)(1) must surely have a substantial effect at least as to some drugs, *see Eli Lilly*, 496 U.S. at 678–79 n.7, whatever else it may do, the legislative history cannot support a broad reading of Section 271(e)(1).

a special exception to the prohibitions of a statute generally rests on one who claims its benefits") (citation omitted).

The legal standard agreed to by the parties[12] and applied by the District Court in the jury instruction reflects these inferences. The instruction provided:

> Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generations of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Consistent with the language of Section 271(e)(1), this instruction did not impose a bright line test. Instead, it directed the jury to determine whether it would have been objectively reasonable for Merck to believe that the infringing experiments at issue would contribute, relatively directly, to

[12] It is too late for Merck to object to the legal standard it proposed for the jury instruction. The version of Federal Rule of Civil Procedure 51 in force at the time of trial in 2000 provided that "[n]o party may assign as error the giving or the failure to give an instruction unless [that party] objects thereto before the jury retires to consider its verdict, stating distinctly the matter to which [that party] objects and the grounds of [that party's] objection." Fed. R. Civ. P. 51. This language is "uncompromising." *City of Newport v. Fact Concerts, Inc.*, 453 U.S. 247, 255 (1981). This Court has refused to review a jury instruction agreed to by a party. *See, e.g., City of Springfield v. Kibbe*, 480 U.S. 257 (1987) (dismissing certiorari as improvidently granted on basis of petitioner's challenge to jury instruction where petitioner agreed to the instruction in the trial court); *City of Monterey v. Del Monte Dunes at Monterey, Ltd.*, 526 U.S. 687, 704 (1999) (ruling that party who "proposed the essence of the instructions given to the jury . . . cannot now contend that the instructions did not provide an accurate statement of the law").

the kinds of information that would be relevant to the drug approval process. The "relatively directly" language reflected the inference from the statute that as an exception it must be narrowly construed; it also reflected the use of the word "solely" in Section 271(e)(1). Finally, the instruction properly placed the burden of proof on Merck, in accordance with the principle that a party invoking a statutory exception has the burden of proving its application.

III. LEGALLY SUFFICIENT EVIDENCE SUPPORTS THE JURY'S VERDICT THAT MERCK FAILED TO CARRY ITS BURDEN OF PROOF UNDER THE FDA EXEMPTION.

A. Merck Ignores the Standard of Review.

Merck requests that this Court enter judgment for it, but fails to identify the relevant rule in the Federal Rules of Civil Procedure or to state the appropriate standard of review.

In considering a Rule 50(a) motion for judgment as a matter of law, the court must "draw all reasonable inferences in favor of the nonmoving party, and it may not make credibility determinations or weigh the evidence." *Reeves v. Sanderson Plumbing Prods., Inc.*, 530 U.S. 133, 150 (2000) (citation omitted). "Credibility determinations, the weighing of evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of a judge." *Id.* (citation omitted). Thus, "although the court should review the record as a whole, *it must disregard all evidence favorable to the moving party that the jury is not required to believe.*" *Id.* at 151 (emphasis added) (citing 9A C. WRIGHT & A. MILLER, FEDERAL PRACTICE AND PROCEDURE § 2529, at 299 (2d ed. 1995)). The standard of review is the same at the trial court level and on appeal. WRIGHT & MILLER, § 2524, at 251.

Because Merck had the burden of establishing the applicability of the FDA Exemption, a court entertaining Merck's Rule 50(a) motion must "test the body of evidence not for its insufficiency to support a finding, but rather for its overwhelming effect." WRIGHT & MILLER, § 2535, at 328 (citing *Mihalchak v. Am. Dredging Co.*, 266 F.2d 875, 877 (3d Cir. 1959)). Thus, "granting a judgment as matter of law for the party bearing the burden of proof is reserved for extreme cases." *Id.* at 325; *see also* 9 J. MOORE ET AL., MOORE'S FEDERAL PRACTICE ¶ 50.05[2] (3d ed. 2004) ("[G]ranting judgment as a matter of law for a party who bears the burden of proof is an extreme step that may be taken only when the evidence favoring the movant is so one-sided that, absent adequate evidentiary response by the non-movant, it could not be disbelieved by a reasonable jury.").

Finally, Rule 50(a)(2) specifies that a motion for a judgment as a matter of law "shall specify . . . the law and the facts on which the moving party is entitled to judgment." Thus, "[c]ontentions not urged in the trial court are not available on appeal," WRIGHT & MILLER, § 2536, at 333, and this Court may not consider evidence or arguments not raised in Merck's initial pre-verdict motion for judgment as a matter of law. *Id.* § 2537, at 344–45 (noting that because a renewed motion for judgment as a matter of law "is nothing more than a renewal of the earlier motion when made at the close of the presentation of the evidence, it cannot assert a ground that was not included in the earlier motion").

To the extent that Merck's merits brief is construed as seeking a sufficiency of the evidence review under Rule 50, it ignores the standard of review by focusing on its evidence and ignoring the evidence favorable to Integra. Merck has offered no reason why the jury could not rely upon the evidence that was favorable to Integra. Finally, Merck ignores the standard of review by asking this Court to assume the role of the jury by weighing the evidence.

B. Merck Assumed Sole Responsibility for Studies Oriented to FDA Requirements and Relegated Scripps to Basic Research Performed Prior to the Commencement of Merck's Drug Development Program.

Merck distinguishes between basic research aimed at selecting a compound and the drug development process. As explained by Dr. Schmitges, Merck's Director of Biomedical Research, Preclinical Pharma Research, "Research program means we try to identify compounds that have activity in this field, whereas development means the testing of such compounds in animals to do toxicology studies and to test them in human beings." J.A. 499. Merck's development programs are focused on regulatory requirements (primarily toxicology and clinical testing in humans), whereas its research programs are not oriented to regulatory requirements. *Id.* Dr. Sombroek, Merck's head of Preclinical Research and Development, testified that under Merck's procedures the transition from research to development is the decision by the Pharma Board to proceed with the development of a specific compound. Docket No. 1027, Ex. 13, at 94–95. Similarly, Merck's Dr. Noll testified that the preclinical phase "begins when the steering committee has designated the project a development project." J.A. 488.

The development process for the infringing RGD compounds began in November 1996, when Merck's Pharma Board approved development of RGD compound EMD-8. J.A. 490. Dr. Noll was appointed the project manager at that time, Docket No. 1027, Ex. 10, at 66, and assumed responsibility for "all of the activities you need to be carried out preclinically and clinically and to present them in a plan and how they fit together." J.A. 494. Merck's Drug Development Group (EPG) met for the first time late that same month. J.A. 493–94; 129–32 (meeting minutes). No one from Scripps was included in any of the EPG core team

meetings or was ever copied on any EPG team meeting minutes. Docket No. 1027, Ex. 10, at 73. Merck alone performed the toxicology, pharmacology, and pharmacokinetic work necessary for FDA approval. J.A. 470, 477–78. Even as late as January 21, 1997, Merck had not yet drafted a development plan for the toxicologic and pharmacokinetic analysis of EMD-8. J.A. 495.

Given that Merck was solely responsible for all FDA-oriented preclinical studies, what was the purpose of Scripps' Merck-funded research? Significantly, when asked to state the reason Merck decided to enter into its 1995 Funding Agreement with Scripps, Dr. Jonczyk made no mention of FDA studies. Docket No. 1027, Ex. 7, at 44–45. Instead, he pointed to the discovery that $\alpha_v\beta_3$ inhibitors have something to do with anti-angiogenesis and to "the fact that we could expand biological and chemical capacity at Scripps." *Id.* at 45. Consistent with these non-FDA purposes, Merck's Dr. Sombroek wrote to Dr. Cheresh that Merck intended to perform the full range of experimentation related to safety—toxicology, pharmacokinetica, pharmacodynamics, and biodistribution—at its own institute in Germany. J.A. 127.

Dr. Cheresh himself told the jury that after August 1995 "we [Scripps] were really searching for an ideal drug candidate." Tr. 1092. Accordingly, many of the infringing experiments carried out by Scripps and Dr. Cheresh used the RGD peptides supplied by Merck as "positive controls" to aid in screening non-RGD organic molecules for biologic activity. J.A. 463–65 (Goodman); J.A. 187–89 (Dedhar). This work was part of the commercial contract between Merck and Scripps, whereby Scripps agreed to screen up to 100 compounds a year for biologic activity. J.A. 89–93. None of these experiments were necessary for generating FDA-related data for the approval of EMD 121974. J.A. 479 (Jonczyk). The peptides were simply used as tools to aid

Merck in the process of screening many nonpeptide compounds in the hopes that one might prove to be a viable drug candidate.

Dr. Cheresh also told the jury that Scripps' preclinical experiments were designed to strengthen the scientific foundation for the basic approach he pioneered of blocking the $\alpha_v\beta_3$ receptor. He explained that "the idea is to have three separate structural distinct compounds do the same thing, and that really bolsters the notion that $\alpha_v\beta_3$ is the thing you want to target, whether you do it with a peptide, whether you do it with an antibody, whether you do it with an organic molecule." Tr. 1128. Scripps' preclinical experiments were also designed to provide grounds for obtaining broader and stronger patent claims. Tr. 1129.

Thus, the evidence is that Merck—and Merck alone—would do the FDA-related preclinical studies, with Scripps assigned to do basic research intended for other goals unrelated to the FDA. Both sides' witnesses agreed that the FDA is not interested in, and does not require, data reflecting an applicant's search for the best drug candidate. J.A. 433–34 (Meyer for Integra); J.A. 480 (Jonczyk for Merck). Further, as discussed below, there is no evidence that Scripps contributed anything to the generation of information above and beyond what Merck was preparing to do on its own. Under these circumstances, the jury's verdict that Merck could not reasonably have believed that Scripps' preclinical work would contribute to the generation of data likely to be relevant to the FDA's decision-making process is well justified. The jury had a sound basis for inferring that Merck was seeking to use the FDA Exemption as a cover for infringing work by Scripps designed to further Merck's non-FDA commercial goals.

C. Merck Failed to Prove That It Would Be Objectively Reasonable for a Party in Merck's Situation to Believe That Scripps' Preclinical Experiments Would Contribute, Relatively Directly, to the FDA's Decision Regarding Safety.

At trial, Merck argued that a total of 114 experiments by Scripps related to safety: Angiogenesis/Chick CAM Assays (85 experiments); Angiomatrigel (2 experiments); cell adhesion assays (25 experiments); chemotaxis (1 experiment); and tumor in SCID mouse assay (1 experiment). S.A. 3–5. Of these, Merck described 89 experiments as pertaining to "inhibition of angiogenesis" (chick CAM assays, angiomatrigel, chemotaxis, and tumor growth in SCID mouse). *Id.* The remaining 25 experiments were described as pertaining to "inhibition of cell adhesion" (cell adhesion assay) and "inhibition of cell migration" (chemotaxis). *Id.*

A party in Merck's position could not reasonably have believed that any of Scripps' infringing experiments were likely to lead to the generation of information relevant to the FDA's assessment of safety. Integra's expert, Mr. Meyer, testified that the FDA's practice is to require that preclinical data for an IND comply with GLP regulations.[13] Merck's witnesses, Drs. Friedlander and Cheresh, confirmed that Scripps' facilities were not GLP-certified. J.A. 245 (Fried-

[13] Integra offered the testimony of Gerald Meyer, a former FDA official with substantial personal experience in the drug approval process, as an expert in that process. Tr. 3159. Even Merck stipulated that Mr. Meyer was an expert "concerning the nature of data required by the FDA for submission to conduct clinical trials in humans pursuant to an IND." Tr. 3159–60. In this Court, neither Merck nor the government challenges either his qualification as an expert on the FDA approval process or the jury's ability to rely on his testimony to reach a verdict. J.A. 426–27.

lander); J.A. 279 (Cheresh).[14] None of Scripps' infringing experiments complied or could have complied with either FDA-mandated standard.

Merck argues that, contrary to Mr. Meyer's testimony, GLP standards do not apply to all preclinical work in advance of an IND. However, companies preparing to submit INDs are advised to "[m]ake sure that all nonclinical tests to support an IND are conducted according to good laboratory practices (GLPs) to avoid raising questions by [the] FDA or creating an initial impression of lack of sophistication or unreliability of the company." HOW TO WORK WITH THE FDA, *supra*, at 2; *see also* A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION, *supra*, at 96 ("[T]he preclinical phase is subject to specific FDA regulations known as good laboratory practices . . . .").

Regardless of whether the FDA's practice of requiring GLP compliance is as strict as Mr. Meyer testified, there is an absolute requirement that submission of non-GLP data for safety purposes must be accompanied by a written explanation of any non-compliance. 21 C.F.R. § 312.23(a)(8)(iii). There is no evidence in the record that Merck or Scripps submitted, or even contemplated submitting, a statement of non-compliance for Scripps' experiments. This omission is powerful evidence that it would not have been objectively reasonable for Merck to believe that Scripps' preclinical experiments would likely be relevant to the FDA's assessment of safety. That is particularly true given that Merck had as-

[14] In the discussion *infra*, Integra notes that the jury was not required to believe the testimony of these witnesses and that, therefore, the District Court was required to disregard their testimony insofar as it was favorable to Merck. The District Court was required, however, to give credence to the evidence favoring Integra, and thus these portions of the witnesses' testimony are relevant.

sumed responsibility for generating safety data for the FDA in-house, without reliance on Scripps.

Mr. Meyer further testified that to substantiate human safety for an IND application, the FDA requires data from experiments in animal species that have some predictive value for human beings. J.A. 428–29. Such species are mice, rats, hamsters, guinea pigs, dogs, and monkeys. J.A. 429. Of the 114 experiments that purportedly relate to safety, 94 were performed on chicken embryos (chick CAM assays). S.A. 3–5. Data from a chicken embryo would not have any value in a safety evaluation because chicken data are not predictive of the human experience. J.A. 429–30. Indeed, the FDA once attempted to use chick CAM assay and the data were unreliable. *Id.* Likewise, Mr. Meyer testified that data generated from cell-adhesion assays (25 experiments; S.A. 3) have no value to the FDA in substantiating safety in humans. J.A. 430–31.

Notably, neither Merck nor the *amici* supporting Merck have challenged Mr. Meyer's testimony in this respect. Nor can they, because at trial Merck's own scientists agreed with Mr. Meyer. Dr. Jonczyk testified that the chick CAM assays are not suitable for drawing inferences with respect to human toxicity. J.A. 481. In fact, he stated that he "could not imagine" that studies on chicken embryos could be permissible. *Id.* Merck's Dr. Luckenbach agreed that the chicken embryo data would not be of any use before the FDA. J.A. 487.

Of the 20 non-chicken experiments that Merck contends are related to safety, 15 are *in vitro* cell adhesion assays. Merck's Dr. Jonczyk testified that he could not imagine that safety inferences based on cell adhesion studies would be appropriate. J.A. 481–82. Significantly, Dr. Cheresh told the jury that he included this assay in his preclinical program because it allows one to choose the best peptide and to avoid selecting a compound that binds to a receptor other than $\alpha_v\beta_3$

so as to negatively affect safety. Tr. 1049–50. There is no testimony that this assay provides information pertinent to safety, as opposed to the hunt for the best drug compound.

D. Merck Failed to Prove That It Would Be Objectively Reasonable for a Party in Its Position to Believe That Scripps' Preclinical Experiments Would Contribute, Relatively Directly, to the FDA's Decision Regarding Efficacy.

Merck's argument that certain of Scripps' preclinical experiments relate to efficacy, S.A. 3–5, fails because of Mr. Meyer's testimony that the FDA relies solely on clinical data to determine efficacy. J.A. 425–26. As discussed below, this uncontroverted testimony is consistent with the applicable statutes and FDA regulations. Moreover, the jury could reasonably have concluded that the majority of the information generated from the infringing experiments was not likely to be relevant to the FDA's efficacy review when it could not be relied upon for safety. Indeed, it defies common sense to argue that data from chicken embryos may have significant bearing on efficacy to humans, given that chicken data are not predictive of human experience. J.A. 429–30.

As noted in the introductory overview of the FDA drug approval process, the FDA considers preclinical data for efficacy only in certain extraordinary circumstances not present in this case. *See* 21 C.F.R. §§ 600, 610(a). Merck and the government repeatedly assert that the FDA reviews preclinical data for efficacy in evaluating an IND application, but upon close examination the authorities they cite for this proposition simply do not support it, and often refute it. For example, Merck argues, "While a primary focus of the IND application is to verify that the proposed human testing is 'reasonably safe,' 21 C.F.R. § 312.23(a)(8), the FDA also requires evidence that 'the compound exhibits pharmacol-

ogical activity that justifies commercial development.'" Merck Br. at 46 (citing FDA, *IND Review Process* 4, *available at* http:// www.fda.gov/cder/handbook/ind.htm). To find the material cited by Merck, one must click on a box labeled "IND" found at the URL provided by Merck.[15] The page to which this link leads reads as follows:

> During a new drug's early preclinical development, *the sponsor's primary goal* is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.
>
> Generally, this includes data and information in three broad areas:
>
> ***Animal Pharmacology and Toxicology Studies***
> Preclinical data to permit an assessment as to whether the product is *reasonably safe for initial testing in humans*.

FDA, *Investigational New Drug Application*, http://www.fda.gov/cder/handbook/indbox.htm (boldface and italics in original; other italics supplied). Contrary to Merck's assertion, the cited FDA web page plainly states that whether "the

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[15] A copy of the graphic found on the web page that Merck cites is attached to this brief as the final page of the addendum to this brief (page 9a). Notably, the graphic makes it clear that all information submitted in an IND is reviewed strictly for "safety."

compound exhibits pharmacological activity that justifies commercial development" is the sponsor's concern, not the FDA's.

Indeed, the remainder of the FDA web page cited by Merck refutes Merck's assertion that the FDA evaluates preclinical pharmacology data for efficacy at the IND stage. As quoted above, the page states that the FDA requires preclinical pharmacology data to "permit an assessment as to whether the product is *reasonably safe for initial testing in humans*." *Id.* (emphasis added).

Next, Merck cites the regulation requiring an IND submission to state "'[t]he rationale for the drug or the research study.'" Merck Br. at 47 (citing 21 C.F.R. § 312.23(a)(3)(iv)). Merck further argues that the "rationale must necessarily rest upon data—from experiments in both animals and test tubes—demonstrating the basis for believing that the drug might have therapeutic value in a particular disease." *Id.* (citing FDA, *Benefit vs. Risk: How CDER Approves New Drugs* 2, http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf). Nothing in this FDA publication, however, states that *preclinical* data are used to evaluate efficacy. Indeed, the cited page affirmatively refutes Merck's argument because it states that "*controlled clinical trials* are especially important because *they provide the only basis, under law, for demonstrating effectiveness*." FDA, *Benefit vs. Risk*, *supra*, at 2 (emphasis added). This is consistent with the regulation providing that the *earliest* efficacy data considered in the drug approval process is the data obtained from Phase 1 *clinical* trials. 21 C.F.R. § 312.21(a)(1).

In any event, 21 C.F.R. § 312.23(a)(3)(iv) requires only an explanation of "the rationale for the drug or the research study." The FDA instructs that this statement be brief, not a compilation of data from experiments. *See* FDA, *Guidance for Industry: Content and Format of Investigational New*

Drug Applications (IND) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products 3 (Nov. 1995) http://www.fda.gov/cder/guidance/phase1.pdf ("Regulations repeatedly describe this section as brief. Ordinarily, two to three pages should suffice. The information requested here is intended to place the developmental plan for the drug into perspective and to help FDA anticipate sponsor needs.").

A comparison with the FDA's corresponding regulation for an NDA application shows that 21 C.F.R. § 312.23(a)(3)(iv)'s request for a drug's "rationale" in an IND submission does not sweep as broadly as Merck claims. The NDA must contain not only a "rationale," but also material that is similar to what Merck claims an IND rationale must contain: "A statement identifying the pharmacologic class of the drug and a discussion of the scientific rationale for the drug, *its intended use, and the potential clinical benefits of the drug product*." 21 C.F.R. § 314.50(c)(2)(ii) (emphasis added).

Merck also cites 21 C.F.R. § 312.23(a)(8) and quotes a portion of the regulation. *See* Merck Br. at 47 (noting "'[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.'"). Merck goes so far as to emphasize the word "pharmacological" in the passage. Merck's quotation, however, omits the critical remainder of the sentence, i.e., "*on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations*." 21 C.F.R. § 312.23(a)(8) (emphasis added). Similarly, Merck quotes and italicizes Section 312.23(a)(8)(i), which requires "[a] section describing the . . . mechanism(s) of action of the drugs in animals, and information on the absorption, distribution, metabolism, and excretion of the drug." Merck Br. at 47 (ellipsis in original). What Merck fails to note, however, is that this material is merely a sub-

section of 21 C.F.R. § 312.23(a)(8). The portion of the introductory sentence quoted above (which Merck omitted) clarifies that Section 312.23(a)(8)(i) *also* pertains to safety.

Finally, Merck argues that the FDA's regulations "require the applicant to submit a draft 'Investigator's Brochure,' which includes evidence of 'the *pharmacological . . . effects* of the drug in animals.'" Merck Br. at 47 (citations to 21 C.F.R. § 312.23(a)(5) and (a)(5)(i) omitted; emphasis added; ellipsis in original). As noted above, Section 312.23(a)(8) explicitly states that for IND purposes, "pharmacological effects" are relevant only to safety. *See also* FDA, *Investigational New Drug Application*, *supra* (defining "animal pharmacology and toxicology studies" as "preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans").

The government's citations for the proposition that an IND submission requires efficacy data likewise do not withstand scrutiny. The government asserts, "The IND must be supported by pre-clinical research regarding the safety *and efficacy* of the drug, including 'pharmacological and toxicological studies of the drug involving laboratory animals or in vitro.'" Gov't Br. at 2 (emphasis added) (citing 21 C.F.R. §§ 312.23(a)(8), (a)(3), and (a)(5)). What is significant is the portion of the regulation that the government omits. The regulation requires "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, *on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.*" 21 C.F.R. § 312.23(a)(8) (emphasis added). By omitting everything after the comma and then throwing in the gratuitous reference to "efficacy," the government's brief misstates the obvious import of the regulation.

The government also argues that at the IND stage, the FDA "considers pre-clinical studies related to effectiveness of a drug in determining whether clinical trials would pose an 'unreasonable risk' to the safety of participants in the trials." Gov't Br. at 10 (citing 21 U.S.C. § 355(i)(3)(B)). Although the statute does state that the test for whether preclinical testing may proceed is "unreasonable risk," it certainly does not require the consideration of preclinical studies or data related to effectiveness. Indeed, the FDA's informal guidance on INDs states that preclinical pharmacological studies should be submitted "[t]o the extent that such studies may be important to address *safety* issues, or to assist in evaluation of toxicology data . . . however, *lack of this potential effectiveness information should not generally be a reason for a Phase 1 IND to be placed on clinical hold.*" FDA, *Guidance for Industry*, *supra*, at 11 (emphasis added).

Moreover, other FDA documents make clear that in practice, the FDA's only concern at the IND stage is safety, which requires that preclinical data submitted be "*nonclinical*," that is, GLP-certified. *See* FDA, *Frequently Asked Questions on Drug Development and Investigational New Drug Applications* 5–6, http://www.fda.gov/cder/about/smallbiz/faq.htm, *reprinted in* Addendum, page 8a.

Finally, even if the government were otherwise correct, and preclinical efficacy data played some role in the FDA's ultimate safety evaluation of an IND based on a risk/benefit calculus, such efficacy data would still have to be GLP-certified, because the data would be used for a *safety* determination. *See* 21 C.F.R. § 312.23(a)(8)(iii); 21 C.F.R. § 58.3.

In sum, what is missing from Merck's and the government's arguments is an appreciation that the IND application process is intended only to determine whether the drug is *safe enough to test in humans*, not whether *the drug accom-*

plishes its intended purpose. The latter is determined by the clinical testing in humans. "Safe enough to test in humans" is determined by looking at the pharmacological effects, as prescribed by 21 C.F.R. § 312.23(a)(8)(i)—that is, when a given amount of the drug is administered to an animal, what happens? Are there any problematic side effects? If so, the drug would not be "safe enough to test in humans."

E. Merck's Witnesses Were Discredited

As noted above, Federal Rule of Civil Procedure 50 required the District Court to *disregard* "all evidence favorable to the moving party [i.e., Merck] that the jury was not required to believe." *Supra* at Part III.A. (quoting *Reeves*, 530 U.S. at 151). Because Integra effectively impeached or contradicted the testimony of Merck's witnesses, the jury was not required to accept their testimony. Therefore, the District Court was correct in disregarding it in considering Merck's motion for judgment as a matter of law.

Merck's and Scripps' witnesses were repeatedly shown not to be credible. Dr. Cheresh's interrogatory responses stated that *all* his work done from 1995 to October 15, 1996, was basic laboratory research undertaken solely for philosophical or scholarly gratification. C.A. App. 15069. Yet, at trial, Dr. Cheresh stumbled, testifying that all of his work from 1995–1998 was done for FDA approval. *See* J.A. 42. The jury was entitled to conclude that because Dr. Cheresh contradicted himself as to portions of his testimony, he should be disbelieved in others as well.

Merck's other key witnesses were similarly exposed as not credible. Dr. Friedlander had specifically sought grant funding to upgrade his laboratory to comply with the GLP requirements because he knew that the IND process would require the repetition of "many of our animal studies" using GLP protocols. S.A. 23. At trial, however, Dr. Friedlander

claimed that he was mistaken and that GLP was actually not required for FDA approval. J.A. 265. Given these contradictions, the jury was not required to believe Dr. Friedlander.

Similarly, Merck's reliance on the conclusory testimony of its FDA expert Dr. Bynum, that all of Scripps' experiments were done to seek FDA approval, is misplaced. Dr. Bynum manifested his bias by his willingness to reach the conclusion that the FDA Exemption applied before he even looked at Scripps' laboratory notebooks or understood the nature of the accused experiments. J.A. 367–68. Dr. Bynum admitted that when he executed a declaration expressing his conclusion on the applicability of the FDA Exemption, he did not even know what a chick CAM assay was. J.A. 368–69. On the stand he also attempted to retract his deposition testimony that the IND application does not require any information beyond mere safety and toxicity. J.A. 376–77.

When asked about the status of Merck's angiogenesis program in 1996, the Director of Biomedical Research, Claus Schmitges, testified (in deposition testimony played at trial) that Merck was in the research phase. Dr. Schmitges testified that there was a distinct difference at Merck between research programs and development programs and that, while development programs were focused on regulatory requirements, research programs were not so oriented, but rather were the start of the project. J.A. 498–99. Although Dr. Schmitges did not appear at trial, Merck had one of his assistants, Dr. Goodman, testify at trial that Dr. Schmitges was "mistaken" and "has been outside the laboratory for rather a long time," notwithstanding Dr. Schmitges's important position at Merck. J.A. 222–23.

In view of these contradictions, the District Court properly disregarded all of this testimony and evidence in considering Merck's motion for judgment as a matter of law.

What is particularly notable is that these discredited witnesses are the only witnesses presented by Merck in support of the idea that the accused experiments relate to efficacy data. As to the following categories of infringing experiments, Merck relies on the testimony of Dr. Cheresh to establish a relationship to efficacy:[16] $\alpha_v\beta_3$-binding assay experiments, S.A. 6; angiogenesis/chick CAM assay experiments, S.A. 6; angiomatrigel experiments, S.A. 6; cell adhesion assay experiments, S.A. 6; cell adhesion assay experiments, S.A. 6; chemotaxis experiments, S.A. 7; FACS experiments, S.A. 7; mice arthritis experiments, S.A. 7; tumor growth chick CAM assay experiments, S.A. 8; tumor growth in SCID-mouse experiments, S.A. 8; and tumor growth/nude mice assay experiments, S.A. 8. Thus, the jury was not required to accept Merck's contention that any of these experiments related to efficacy, and the District Court was therefore required to ignore all of this testimony.

Similarly, as to mice-retina-vasculo experiments, S.A. 7, and rabbit cornea assay experiments, S.A. 8, Merck relies on the testimony of Dr. Friedlander. As noted above, Dr. Friedlander discredited himself through inconsistent testimony, and therefore the jury was not required to believe him and, in assessing the JMOL, the District Court was required to disregard his testimony.

F. Merck's Other Evidence Was Insufficient to Require a Finding in Merck's Favor.

Before reviewing Merck's other evidence, it should be noted that Merck's legal department also encouraged scientists to draft documents during this litigation to make the FDA approval process appear more imminent for purposes

[16] Dr. Cheresh, as noted above, discredited himself through inconsistent testimony.

of a pretrial motion for summary judgment. S.A. 39–40. The Merck scientist to whom the request was made initially balked, noting in a memorandum to his supervisor that he could not comply with the demands of Merck's legal department to generate a development plan since important data from toxicology and pharmacology were lacking. J.A. 459–60. He felt it would be unacceptable to submit a draft, even though it could assist in the litigation, because it would ultimately impugn Merck's credibility. *Id.* Dr. Noll of Merck testified that prior to January 21, 1997, there was *no* toxicologic or pharmacokinetic analysis of EMD-8 and there was no preclinical plan. J.A. 495.

Merck argues that it became objectively reasonable in March 1994 for Merck and Scripps to view the Scripps experiments as generating data for the FDA review process. *See* Merck Br. at 44–45. Merck never asserted this argument in its JMOL (or its renewed JMOL, for that matter) in the District Court. Hence, this entire argument has been waived. *See* Fed. R. Civ. P. 50(a)(2).

Merck's reliance, Merck Br. at 19, on information contained in the IND submitted by another company, Ixsys, is also based on the faulty assumption that anything that an infringing company chooses to place in an IND application must necessarily be objectively relevant to the FDA approval process. Section 271(e)(1) includes the requirement that the activities be "reasonably" related to the FDA approval process. Without this objective standard, virtually anything an infringer includes in the IND's background section could be considered related to the FDA approval process. Notably, even the government recognizes that the mere inclusion of information in an IND does not necessarily make the information relevant: "[T]he law should not be construed to create an artificial incentive to include irrelevant information in an IND, and a researcher should not be able to immunize itself from infringement by including such experiments in an

IND." Gov't Br. at 24. Thus, the District Court correctly found that this evidence was insufficient to mandate a verdict in favor of Merck.

Finally, Merck argues that Dr. Cheresh had discussions with the FDA on behalf of Merck regarding the types of experiments needed to convince the FDA to allow clinical trials. Merck Br. at 19. However, Merck's own witnesses testified that the FDA played no role in experimental design, or in the preparation of the draft IND application. J.A. 467–69. Indeed, when asked, "What input if any have you received from the FDA in the course of carrying out your work in preparing the IND application?" Merck's Dr. Grimm said, "We have to this point not received any information from the FDA, as far as I recall." J.A. 472. Notably, Integra's FDA expert, Mr. Meyer, testified that all preclinical meetings with the FDA are recorded. He explained that the regulations specifically require that discussions be incorporated into a written memorandum. J.A. 432. No such memoranda were ever produced by Merck, Scripps, or Dr. Cheresh to support their testimony that the FDA approved everything they did in advance. The jury rightly disregarded this testimony from the discredited Dr. Cheresh.

CONCLUSION

For the reasons stated above, the judgment of the Federal Circuit should be affirmed.

March 22, 2005 Respectfully submitted,

Mauricio A. Flores
McDermott Will & Emery LLP
18191 Von Karman Avenue
Suite 400
Irvine, CA 92612
(949) 851-0633

David M. Beckwith
McDermott Will & Emery LLP
4370 La Jolla Village Drive
San Diego, CA 94304
(858) 535-9001

Raphael V. Lupo
Counsel of Record
Cathryn Campbell
Mark G. Davis
M. Miller Baker
Richard B. Rogers
McDermott Will & Emery LLP
600 13th Street, N.W.
Washington, D.C. 20005
(202) 756-8000

Attorneys for Respondents

ADDENDUM

Federal Rule of Civil Procedure 50(a) and (b)

Rule 50. Judgment as a Matter of Law in Jury Trials; Alternative Motion for New Trial; Conditional Rulings.

(a) Judgment as a Matter of Law.

(1) If during a trial by jury a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue, the court may determine the issue against that party and may grant a motion for judgment as a matter of law against that party with respect to a claim or defense that cannot under the controlling law be maintained or defeated without a favorable finding on that issue.

(2) Motions for judgment as a matter of law may be made at any time before submission of the case to the jury. Such a motion shall specify the judgment sought and the law and the facts on which the moving party is entitled to the judgment.

(b) Renewing Motion for Judgment After Trial; Alternative Motion for New Trial.

If, for any reason, the court does not grant a motion for judgment as a matter of law made at the close of all the evidence, the court is considered to have submitted the action to the jury subject to the court's later deciding the legal questions raised by the motion. The movant may renew its request for judgment as a matter of law by filing a motion no later than 10 days after entry of judgment—and may alternatively request a new trial or join a motion for a new trial under Rule 59. In ruling on a renewed motion, the court may:

(1) if a verdict was returned:

(A) allow the judgment to stand,
(B) order a new trial, or
(C) direct entry of judgment as a matter of law; or

(2) if no verdict was returned:

(A) order a new trial, or
(B) direct entry of judgment as a matter of law.

21 C.F.R. § 312.22 General principles of the IND submission.

(a) FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

(b) The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the objectives described in paragraph (a) of this section depends upon such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

(c) The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate. Annual reports to the IND should serve as the focus for reporting the status of studies being conducted under the IND and should update the general investigational plan for the coming year.

(d) The IND format set forth in §312.23 should he followed routinely by sponsors in the interest of fostering an efficient review of applications. Sponsors are expected to exercise considerable discretion, however, regarding the content of information submitted in each section, depending upon the kind of drug being studied and the nature of the available information. Section 312.23 outlines the information needed for a commercially sponsored IND for a new molecular entity. A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format, but ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. A sponsor-investigator who uses an investigational drug not subject to a manufacturer's IND or marketing application is ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

21 C.F.R. § 312.23 IND content and format.

(a) A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Investigational New Drug Application" (IND) including, in the following order:

(1) *Cover sheet (Form FDA-1571).* * * * *

(2) *A table of contents.*

(3) *Introductory statement and general investigational plan.* * * *

(4) [Reserved]

(5) *Investigator's brochure.* If required under §312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or

special monitoring to be done as part of the investigational use of the drug.

(6) *Protocols.* (i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with §312.30(a).) In general, protocols for Phase 1 studies may he less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

* * * *

(7) *Chemistry, manufacturing, and control information.*
* * * *

(8) *Pharmacology and toxicology information.* Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin

the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology.* (*a*) An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iii) For each nonclinical laboratory study subject to the good laboratory practice regulations under part 58, a statement that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(9) *Previous human experience with the investigational drug.* * * *

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. * * *

(11) *Relevant Information.* If requested by FDA, any other relevant information needed for review of the application.

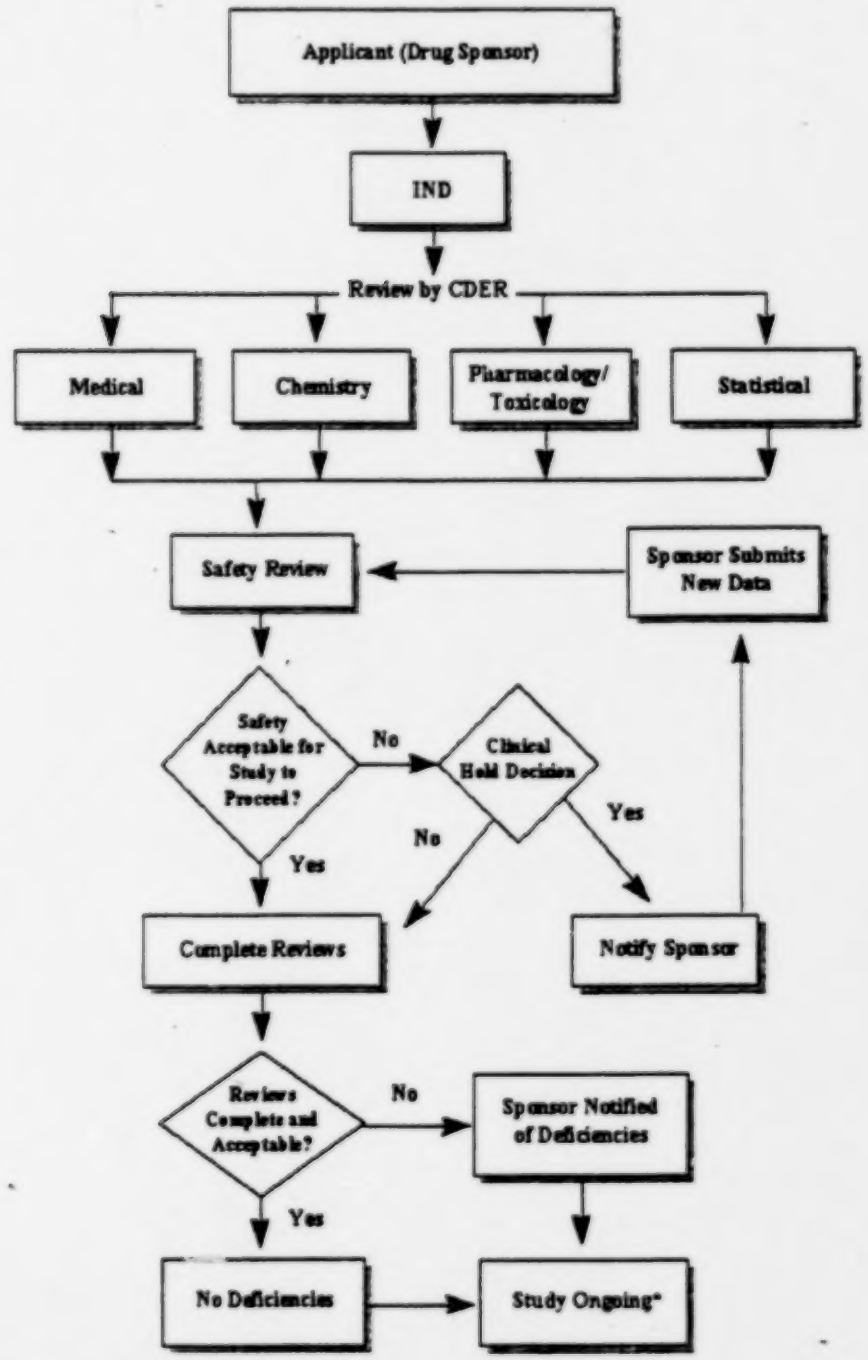
Excerpt from FDA, *Frequently Asked Questions on Drug Development and Investigational New Drug Applications* 5–6, http://www.fda.gov/cder/about/smallbiz/faq.htm:

Investigational New Drug Application

What are the FDA requirements for pre-clinical studies? Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies. Depending on whether the compound has been studied or marketed previously, the sponsor may have several options for fulfilling this requirement: (1) compiling existing nonclinical data from past in vitro laboratory or animal studies on the compound; (2) compiling data from previous clinical testing or marketing of the drug in the United States or another country whose population is relevant to the U.S. population; or (3) undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

IND Review Process

Click any of the following boxes



(Copied from http://www.fda.gov/cder/handbook/ind.htm)